Per-subject characterization of bolus width in Pulsed Arterial Spin Labeling using Bolus Turbo Sampling (BoTuS)

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Word count: 2814

Key words: Brain perfusion, Arterial Spin Labeling, QUIPSS, TI1, bolus width, hypercapnia

Abstract

Quantitative measurement of cerebral blood flow using QUIPSS II pulsed arterial spin labeling relies on the assumption that the time between label and QUIPSS saturation is shorter than the natural temporal bolus width. Yet, the duration of the bolus of tagged blood spins entering the region of interest may vary across subjects due to physiological differences in blood velocity or vessel geometry. We present a new technique, Bolus Turbo Sampling (BoTuS), to rapidly measure the duration of the inflowing bolus. This allows optimizing the ASL acquisition for each subject to ensure reliable quantification of perfusion while maximizing SNR by avoiding the use of unnecessarily short label durations. The repeatability of this technique is evaluated and its validity assessed by comparison with ASL data acquired at variable TI_1 and by testing subjects at different physiologic states.

Introduction

Arterial Spin Labeling (ASL) is a quantitative MRI method to non-invasively measure cerebral blood flow (CBF)[1]. The longitudinal magnetization of water spins in arterial blood is inverted in the feedings arteries and subsequently the flowing tagged spins are imaged in the region of interest after a certain delay (TI_2). ASL methods can be divided into continuous and pulsed ASL (PASL) techniques depending on the way spins are tagged. PASL is widely used in clinical research protocols due to its ease of implementation, its lower specific absorption rate (SAR) and the absence of need for specific coils. The ASL signal depends not only on CBF but also on factors such as magnetization at equilibrium, tagging efficiency, temporal width of the bolus of tagged spins (τ) and the transit time of blood from the label slab to the imaging slice[2]. The QUIPSSII[3] and Q2TIPS[4] sequences aim to eliminate sensitivity to bolus duration and transit times by saturating the longitudinal magnetization of labeled spins remaining in the label region after a delay TI_1. This delay, if shorter than the natural bolus duration, defines the temporal width of the bolus. However, if the saturation is applied too late, the actual temporal width of the bolus is shorter than TI_1, leading to errors in the quantification of CBF from the ASL signal[5].

One response to this issue are multi-TI ASL techniques like QUASAR[6] or Bolus-tracking ASL[7]. Since images are acquired at different inversion times, transit delay and bolus duration can be obtained and accounted for by fitting model functions to the ASL signal. However, multi-TI acquisitions require significantly longer acquisition times or limit the spatial coverage available, and require more sophisticated analysis techniques to obtain robust CBF maps.

Previous single-TI studies have tried to use optimal values for the saturation delay TI_1, fixed for all subjects in a study. However, its dependence on patient population, geometrical label

width and position of the label pulse implies that this optimization may need to be performed for each specific study[8]. Furthermore, if quantitative CBF measurements are to be guaranteed, the shortest natural bolus duration occurring in the patient population dictates the choice of the TI_1 for all subjects, leading to a loss in sensitivity in subjects with longer label durations.

The aim of this study is to validate a new technique (BoTuS, for Bolus Turbo Sampling) to measure the natural bolus duration τ in each subject and thus to optimize the TI_1 parameter individually[9], [10]. This technique directly traces the bolus of the tagged spins for about three seconds after the application of the tag pulse, with a temporal resolution of fifty milliseconds. The initial shape of the bolus of the tagged spins is modeled as a boxcar function with flow through the vasculature modeled as a Gaussian dispersion of the tag in time[11], a modified version of the Hrabe-Lewis model[12], [13].

Methods

For this study, a total of thirteen healthy volunteers (age 23-40 years, five female) were scanned on a 3-T Philips Achieva TX whole body scanner using whole-body RF transmit and 8-channel head receive coils. The institutional review board approved the protocol and all subjects gave prior written consent to participate in the study. During all acquisitions we recorded physiological parameters of our subjects ($EtCO_2$, SpO_2, respiratory frequency, heart rate) to verify that the subjects stayed in the same physiological state. The entire protocol consisted of two parts: 1) the measurement of the shape of the bolus using the BoTuS technique, performed twice under baseline physiologic conditions, once at the beginning and once towards the end of each session in order to assess repeatability, and performed once during globally increased CBF under hypercapnia at the end of the session 2) a different

measurement of the natural duration of the bolus from multi-TI_1 data, to obtain an independent measure of bolus width.

BoTuS protocol

The purpose of this part of the study was to assess the feasibility and the repeatability of the BoTuS technique. The aim of this sequence is to rapidly measure the bolus shape of the tagged spins entering our region of interest (ROI). The BoTuS sequence consists of a PICORE[3] tagging scheme (tag width=200 mm, label gap=15 mm) immediately followed by a rapidly repeated EPI read-out on one axial slice just above the Circle of Willis scanned every 50 ms until TI=2900 ms (Figure 1a). Acquisition parameters were: flip angle=90°, TE=19 ms, EPI BW=3525 Hz, voxel size=4*4*5 mm, NA=10 ctl-tag pairs, total scan duration=1'18". The 90° flip angle assures that the signal is dominated by fresh spins entering the slice between consecutive acquisitions. At a TR of 50 ms in a 5-mm slice, blood in the arteries crossing the slice is fully replaced at flow speeds above 10 cm/s. This is long enough to be sure that fresh blood arrives between subsequent EPI acquisitions in the major feeding arteries of the brain (V_{PCA} > 20cm/s[14]). The mean difference image from the 10 control-tag pairs shows the inflowing bolus in large vessels at each TI. During the protocol we acquired a total of three BoTuS datasets. Two were acquired at baseline physiologic conditions separated by 40 min to test for repeatability. We also tested the capacity of the BoTuS sequence to detect the global flow differences after a vasodilator paradigm using increased $fiCO_2$ (8% CO_2, 21% O_2, balance N_2 administered at approximately 12 l/min via a non-rebreathing face mask). We acquired the hypercapnia BoTuS dataset during CO_2 inhalation, shortly after the second baseline BoTuS dataset.

MATLAB® (The Mathworks, Inc., Natick, MA, USA) was used for the post-processing of the

data. The mean difference between control and tag images was calculated to obtain a vascular ASL signal map at each TI. Using the Brain Extraction Tool (bet2) from FSL[15] data from non-brain tissue were eliminated. To automatically select voxels with arterial signal, four large regions approximately corresponding to anterior cerebral artery (ACA), posterior cerebral artery (PCA), and left and right middle cerebral artery (MCA) vascular territories were defined (Figure 1b). The area under the bolus curve (AUC) was computed for each voxel and voxels with at least 20% of the maximal AUC in each territory were selected. The cluster of connected voxels with the highest cumulative AUC in each of the four vascular territories was retained as ROI for the subsequent analysis. We fitted the bolus in each voxel from each ROI with the model of Ozyurt [I] based on a modified version of Hrabe-Lewis model to account for the dispersion of the labeled bolus[11] (Figure 1c):

[I] $$\Delta M(t) = Ae^{-\frac{t}{T_{1B}}}\left(erf\left(\frac{\tau + \delta t - t}{k\sqrt{t}}\right) - erf\left(\frac{\delta t - t}{k\sqrt{t}}\right)\right)$$

where A is an amplitude factor, T_{1B} is the T_1 of the arterial blood, τ is the natural width of the bolus of tagged spins, δt is the transit delay between label region and imaging slice and k is the dispersion constant. A four-parameter fit was performed using the Levenberg-Marquardt algorithm[16], adjusting A, τ, δt and k on a per-voxel basis.

After averaging the model curves from each voxel of the ROIs, we extracted the full width at half-maximum from the average bolus model curve, taking into account the T_1 decay (Figure 1c). We thus obtain a value of the bolus width for each of the four ROIs from each BoTuS dataset.

Multi-TI_1 ASL protocol

In order to independently measure the duration of the bolus of labeled blood, we measured and analyzed the ASL signal as a function of TI_1, at constant TI_2. The ASL signal in a QUIPSS II sequence is directly proportional to the quantity of labeled blood that leaves the label region prior to TI_1. Blood flow can be assumed to be constant during the TI_1 period, if signals are averaged over many repetitions that are not synchronized to cardiac phase[17]. If TI_1 is shorter than or equal to the natural duration of the bolus, the ASL signal increases linearly as a function of TI_1. For longer TI_1 delays, the ASL signal is independent of TI_1, as all labeled blood has left the label region prior to the saturation pulse. This provides an independent means of measuring the natural duration of the bolus of labeled spins. More standard multi-TI_2 ASL signal measurements also provide information about the label width, but they depend in addition on transit delay, which makes the data less robust to analyze.

We acquired a series of 12 PASL datasets varying the TI_1 from 200 ms to 1300 ms in 100 ms increments in a Q2TIPS sequence in randomized order. ASL acquisition parameters were: EPI single shot images, voxel size [4-4-5 mm], 14 slices, 30 pairs of images, tag width=200 mm, label gap=15 mm, TE=24 ms, total acquisition time ~40 min. The minimum TI_2 was fixed to 1800 ms. TR and TI_2 were mostly independent of TI_1, but needed to be adapted for the shortest and longest TI_1-values due to sequence timing constraints. The exact parameter values used are listed in Table 1. For subjects 11-13 we added measurement points at TI_1= 1600 and 2000 ms and used a SENSE factor 2.5 with a TE of 19 ms. The first slice of the ASL acquisitions is the same as the BoTuS slice (Figure 2a). We acquired a high-resolution T_1-weighted structural image to obtain grey and white matter masks using SPM8 (3D GRE TR=8.1 ms, TE=3.8 ms. voxel size [1-1-1.3 mm], 256 mm field of view, 100 contiguous sagittal slices).

All images were realigned, coregistered to the anatomic image and normalized to the MNI ICBM atlas using SPM8 software (SPM, Wellcome Department of Imaging Neuroscience,

http://www.fil.ion.u-cl.ac.uk/spm/). Control and label images were subtracted. Data acquired at a TI_2 different from 1800 ms were corrected for T_1-decay assuming an arterial blood T_1 of 1700 ms[18]. We calculated the average ASL data from the grey matter in MCA, ACA and PCA territories, for each of the 12 acquisitions (Figure 2b). We then plotted the ASL signal as a function of the TI_1 and fitted it with the model of Ozyurt integrated over time. To determine $TI_{1,max}$, the highest TI_1 acceptable for ASL data acquisition according to the multi-TI_1 data, we located the point beyond which the model curve was outside a 10% margin around the initial linear slope (Figure 2c).

Results

BoTuS protocol

The acquisition time of the BoTuS sequence is 78 seconds. Subsequently, about 2 minutes of processing are required to obtain the bolus width in the four vascular territories. From the 104 measurements we made under baseline physiologic conditions, 12 were excluded due to an insufficient quality of fit (R^2<0.9). Capnia remained constant throughout all acquisitions under baseline condition.

The differences between the bolus width in the left and right MCA and the ACA for our 13 subjects are not statistically significant (right MCA=(708±121) ms; left MCA=(743±116) ms; ACA=(811±156) ms - mean±std), with a higher inter-individual variability in the ACA territory. However, we measured significantly longer bolus duration in the PCA territory: (1094±211) ms. The mean bolus widths for right and left MCA territories for each subject are spread from 550 ms to 977 ms.

We tested the repeatability of the technique by measuring the bolus shape twice, at an interval of 40 minutes. The repeatability is good as shown in the Bland-Altmann[19] scatter-plot (Fig 3). One subject out of thirteen showed a difference to mean exceeding the 2σ-interval. The mean difference between the two measurements is significantly different from zero, which implies the presence of an order-effect.

The repeatability coefficient[19] for the measurement of the average bolus width in the right and left MCA territories is 75 ms, that is, the absolute difference between two repeated measurements is expected to be smaller than this value in 95% of the cases. With a mean bolus width of 728 ms in right and left MCA territories for our 26 measurements, this represents a difference of 10% between two measurements on the same subject. The minimum of the bolus widths in left and right MCA territories (instead of their average) showed the same repeatability.

The mean MCA bolus width in 12 subjects (1 subject was excluded due to an insufficient quality of fit (R^2<0.9)) was (498±176) ms under hypercapnia (HC) and (747±113) ms under normocapnia (NC) immediately prior to the HC experiment. The analyses of the physiological parameters of our subjects showed no significant difference before and during HC in heart rate (NC=(61±7) min^{-1} ; HC=(62±7) min^{-1}), arterial oxygen saturation (NC=(98±1)% ; HC=(98±1)%) and respiratory rate (NC=(15±3) min^{-1} ; HC=(15±3) min^{-1}). The mean end-tidal CO_2 increased from (46±6) mmHg during normocapnia to (57±6) mmHg under hypercapnia. If we assume that the observed reduction in bolus width is inversely proportional to the perfusion change then the mean increase in perfusion due to the CO_2 paradigm was (6±4.3) %/mmHg which is consistent with the literature[20]. The responses to this stimulus were however very heterogeneous between subjects.

Multi-TI_1 ASL protocol

Five subjects were excluded due to excessive motion or because the quality of the fit was bad due to a poor signal to noise ratio (R^2<0.9). The mean $TI_{1,max}$ on the remaining 8 subjects is (1020±182) ms for the right and left MCA territories, (1009±250) ms for the ACA territory and (1152±435) ms in the PCA territory. The differences between the three territories are not significant. Also the values in the PCA territories are very heterogeneous and calculated on two subjects only since the others showed a R^2 lower than 0.9.

Correlation between BoTuS results and multi-TI_1 data

We saw a significant correlation between the bolus width measured in the MCA territory using BoTuS method and the $TI_{1,max}$ determined from multi-TI_1 data, with a Pearson coefficient of 0.65 ($p<0.05$) (Figure 4a). The bolus width derived from the pre-scan under-estimated the allowable TI_1 obtained by the multi-TI_1 method, as attested by the scatter plot.

Discussion

The rapid bolus shape pre-scan (acquisition time of 1'18") allowed determining an optimized TI_1 for each subject. The pre-scan acquisition time is dramatically reduced compared to the 40 minutes of acquisitions needed to obtain the bolus width using the 12 PASL multi-TI_1 data points. There are significant differences in the measured bolus widths between vascular territories. Indeed, the PCA are predominantly fed by the basilar arteries, which exhibit slower flow than the ICA predominantly feeding the MCA[21]. This slower velocity generates a longer bolus. The higher inter-individual variability that we observed on the ACA territories is certainly due to the heterogeneities of the ROI in that region. The right and left

MCA territories are the most homogeneous regions since we selected the middle cerebral arteries just above the circle of Willis. The repeatability of the BoTuS technique in this territory is good as shown in the Figure 3.

The estimation of the allowable TI_1 from the multi-TI_1-data is taken as a reference since it directly samples the ASL signal of interest. However, it suffers from low SNR. The long acquisition times make the results prone to motion artifacts and prevented us from assessing its repeatability. Almost 40% of the multi-TI_1-data had to be discarded. To somewhat alleviate the problem of SNR, and because the bolus duration is shorter in this territory, we used the large MCA territories (≈2400 voxels on average) to examine the correlation with the BoTuS method. The results in the ACA and PCA territories are more variable due to the small ROIs, given the position of the imaging volume above the circle of Willis (≈950 and ≈290 voxels, respectively).

The significant correlation between the BoTuS and the multi-TI_1 methods indicates that our BoTuS sequence has the potential for optimizing PASL acquisitions. However, the BoTuS results are not immediately comparable to the multi-TI_1 data, since the $TI_{1,max}$ is a measure of the integral under the bolus curve. A calibration is therefore necessary to translate the width at half maximum of the roi-average bolus model to a subject-optimized TI_1. The limited multi-TI_1 data available in this study leads us to an empirical calibration: $TI_{1,sequence}=1,2*TI_{1,BoTuS,MCA}$ (Figure 4b).

The bolus widths measured by multi-TI_1 PASL in the MCA territory with a 200-mm label region vary from 717 ms to 1226 ms. With the choice of a fixed TI_1 of 700 ms, perfusion would be quantified accurately for all of our subjects under baseline physiologic conditions. If we determine a per-subject TI_1 using the rapid BoTuS pre-scan and our calibration, one BoTuS scan in one subject may suffer from under-estimation of the perfusion by about 11%.

On the other hand, with TI_2=1800 ms, the optimized TI_1 would lead to an average gain of 18% in ASL signal, with respect to the fixed TI_1 of 700 ms.

The ASL literature is relatively sparse in data concerning the optimal choice of TI_1 depending on label width, position, and subject population. From the limited data presented here it is obvious that inter-subject heterogeneity in label duration is large. The method presented has the potential to avoid the need for time-consuming optimizations of this parameter, and to render protocols more robust to variations in slice positioning and subject physiology and morphology.

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Tables and Figures

TI_1 (ms)	200	300	400	500	600	700	800	900	1000	1100	1200	1300	1600	2000
TI_2 (ms)	1800	1800	1800	1800	1800	1800	1800	1800	1800	1900	2100	2100	2300	2700
ΔTI (ms)	1600	1500	1400	1300	1200	1100	1000	900	800	800	900	800	700	700
TR (ms)	3500	3400	3300	3200	3100	3000	3000	3000	3000	3000	3100	3000	3000	3400

Table 1. Acquisition parameters of multi-TI_1 images (TI_1: Time between label and QUIPSS saturation, TI_2: time between label and acquisition of the first slice, ΔTI=time between saturation and acquisition (TI_1+ΔTI=TI_2), TR: time between successive tag and control label pulses)

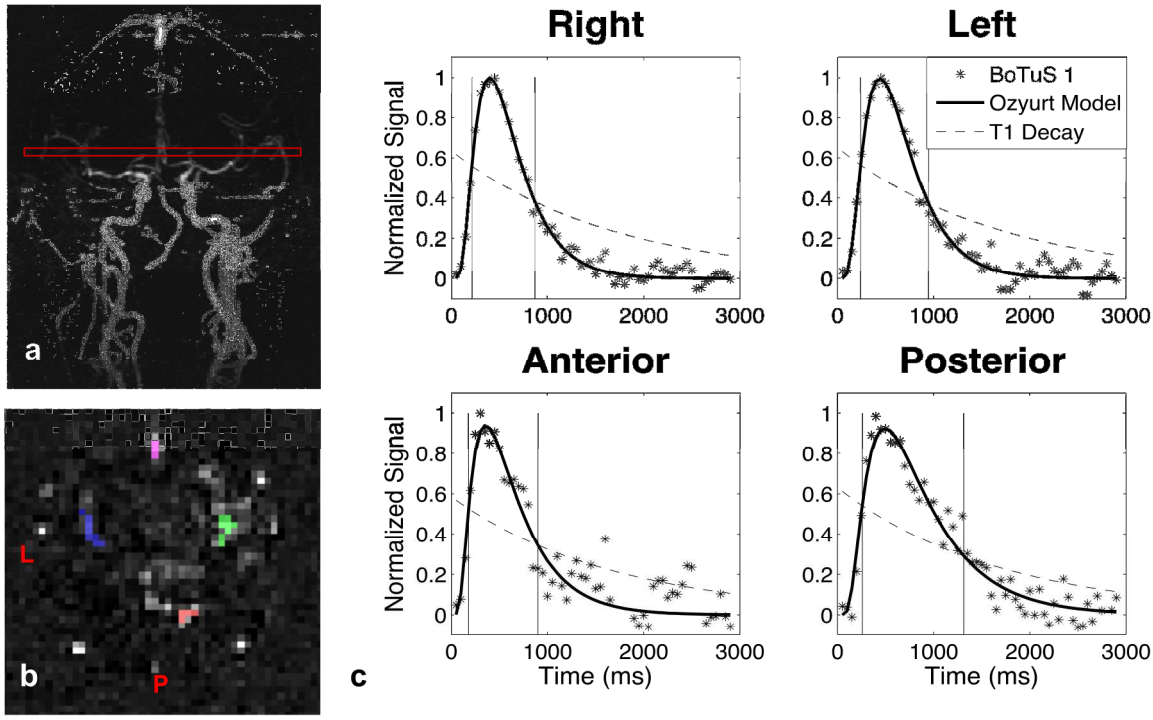

Figure1: a) Position of the BoTuS acquisition slice just above the circle of Willis, b) ROIs of connected voxels with strong vascular signal in right and left middle cerebral arteries, and in the anterior and posterior area, c) Normalized

control/tag difference from the BoTuS sequence showing the bolus shape of the tagged spins entering our regions of interest for four vascular territories. The dashed line indicates the cutoff at half the peak amplitude after correction for T_1-decay, used to determine the duration of the bolus as indicated by the vertical lines.

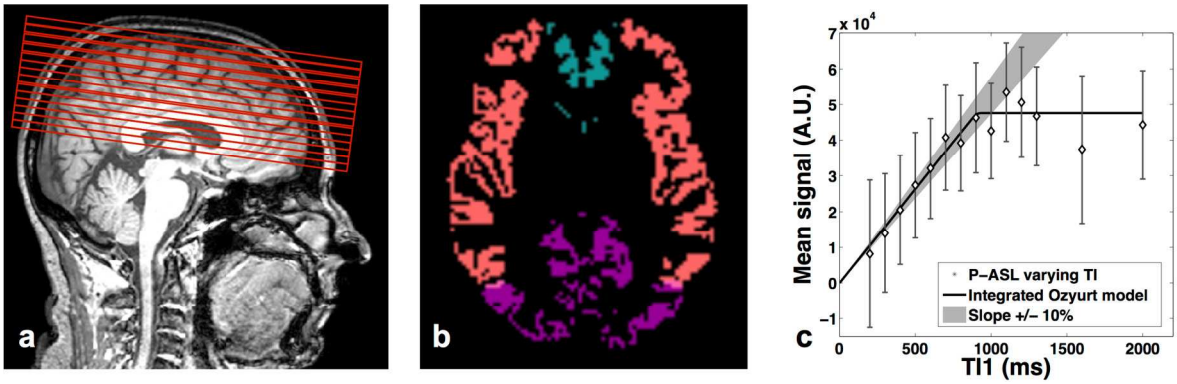

Figure 2: a) Position of the multi-TI_1 imaging slices. The first slice of the PASL region of interest is the same as the BoTuS slice, b) Vascular territory map (pink: middle cerebral arteries, blue: anterior cerebral arteries, purple: posterior cerebral arteries), c) Average ASL signal in the gray matter of the MCA territories as a function of TI_1 for a single subject. The solid line represents the fit to the data and the shaded region indicates the limits of the linear regime of the ASL signal.

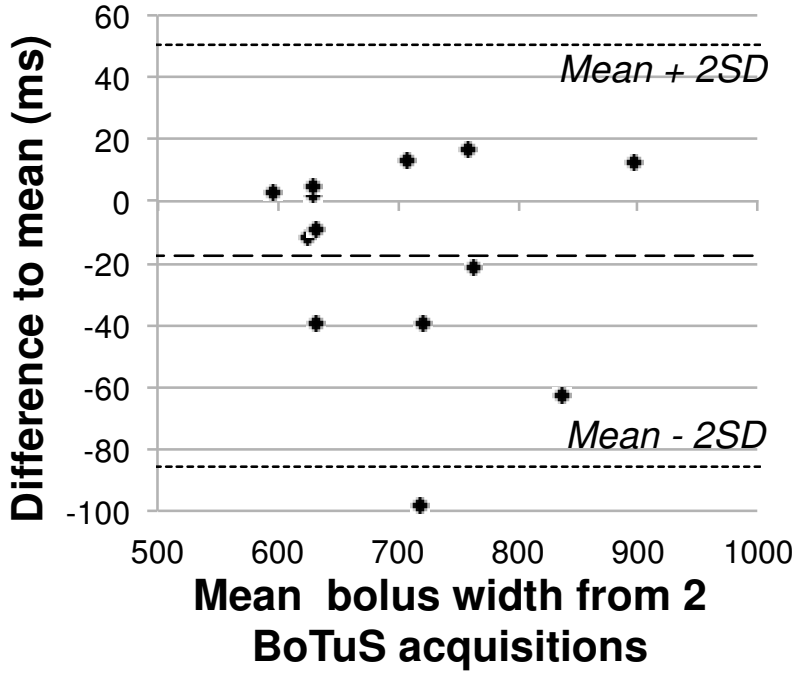

Figure 3: Repeatability of the BoTuS results shown in a Bland-Altmann graph representing the difference to the mean for two separate measurements as a function of their mean.

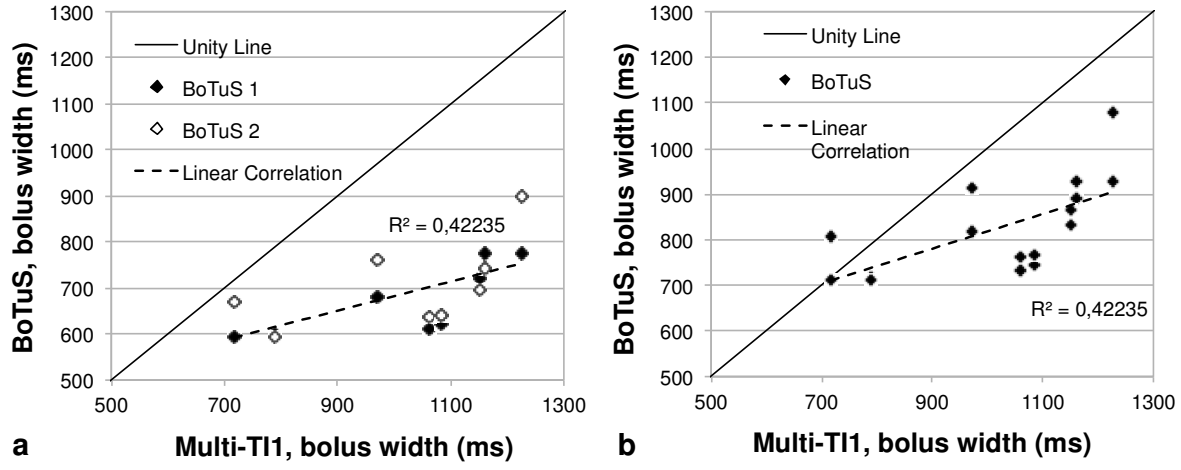

Figure 4: a) Correlation between the bolus width measured twice using BoTuS and using multi-TI_1 PASL for 8 subjects with linear correlation and unity line, b) Correlation between the bolus width measured using BoTuS after correction ($TI_{1,sequence}$=1,2 * $TI_{1,BoTuS}$) and multi-TI_1 PASL method for 8 subjects.